Patients’ and Providers’ Perspectives of a Polypill Strategy to Improve Cardiovascular Prevention in Australian Primary Health Care

A Qualitative Study Set Within a Pragmatic Randomized, Controlled Trial

Hueiming Liu, MBBS, MIPH; Luciana Massi, BBusComm, MIPH; Tracey-Lea Laba, BPharm, PhD; David Peiris, MBBS, MIPH, PhD; Tim Usherwood, BSc, MBBS, MD; Anushka Patel, MBBS, SM, PhD; Alan Cass, BA, MBBS, PhD; Anne-Marie Eades, BN, MN; Julie Redfern, BAppSc, BSc, PhD; Noel Hayman, BAppSc, MBBS, MPH; Kirsten Howard, MApSci(Biopharm), MPH, MHlthEcon, PhD; Jo-anne Brien, BPharm BS (Pharm), PharmD; Stephen Jan, PhD

Background—This study explores health provider and patient attitudes toward the use of a cardiovascular polypill as a health service strategy to improve cardiovascular prevention.

Methods and Results—In-depth, semistructured interviews (n=94) were conducted with health providers and patients from Australian general practice, Aboriginal community-controlled and government-run Indigenous Health Services participating in a pragmatic randomized controlled trial evaluating a polypill-based strategy for high-risk primary and secondary cardiovascular disease prevention. Interview topics included polypill strategy acceptability, factors affecting adherence, and trial implementation. Transcribed interview data were analyzed thematically and interpretively. Polypill patients commented frequently on cost-savings, ease, and convenience of a daily-dosing pill. Most providers considered a polypill strategy to facilitate improved patient medication use. Indigenous Health Services providers and indigenous patients thought the strategy acceptable and beneficial for indigenous patients given the high disease burden. Providers noted the inflexibility of the fixed dose regimen, with dosages sometimes inappropriate for patients with complex management considerations. Future polypill formulations with varied strengths and classes of medications may overcome this barrier. Many providers suggested the polypill strategy, in its current formulations, might be more suited to high-risk primary prevention patients.

Conclusions—The polypill strategy was generally acceptable to patients and providers in cardiovascular prevention. Limitations to provider acceptability of this particular polypill were revealed, as was a perception it might be more suitable for high-risk primary prevention patients, though future combinations could facilitate its use in secondary prevention. Participants suggested a polypill-based strategy as particularly appropriate for lowering the high cardiovascular burden in indigenous populations.

Clinical Trial Registration—URL: http://www.anzctr.org.au. ANZCTRN: 12608000583347. (Circ Cardiovasc Qual Outcomes. 2015;8:301-308. DOI: 10.1161/CIRCOUTCOMES.115.001483.)

Key Words: adherence ■ qualitative research

Cardiovascular disease is a major cause of mortality and morbidity worldwide and is projected to be the leading cause of death in 2030.1,2 A major part of the problem is large treatment gaps globally—for instance, audits of primary healthcare in Australia indicated that prescription of guidelines-recommended therapy is as low as 50%.3,4 Nonadherence to the treatment is likely to further extend this treatment gap because it is estimated that ≤50% of patients in high-income countries do not adhere to prescribed cardiovascular disease (CVD) medications, with similar suboptimal adherence in low- and middle-income countries.5,6 The reasons for nonadherence fit into well-recognized categories—health
WHAT IS KNOWN

- Although effectiveness trials have shown a significant improvement in patient medication use with a specific polypill formulation (a combination of a statin, 2 blood pressure lowering agents, and anti-platelet agent) when compared with usual care for high-risk primary and secondary CVD prevention, patients’ and providers’ perspectives of this approach are unknown.

WHAT THE STUDY ADDS

- After conducting qualitative interviews with both providers and patients involved in a pragmatic clinical trial in Australia, we found general acceptability of the polypill-based strategy with patients reporting greater convenience and cost savings with the polypill.
- However, some prescribers highlighted limitations of this particular formulation in regards to dosage inflexibility and recommended that more dosage combinations be made available.

This pragmatic trial was conducted in a variety of primary healthcare services across Australia in urban, rural, and remote settings, thereby maximizing potential generalizability and sought to improve patient medication use and the prescribing of indicated therapy for high-risk primary and secondary CVD prevention patients. Significantly, in Australia where indigenous patients have a higher burden of CVD, the trial was conducted in accessible and culturally safe indigenous health services.

Primary outcomes were measured by self-reported medication use and changes in biological markers of changes in systolic blood pressure and total cholesterol. Results showed that “After a median of 18 months, the polypill-based strategy was associated with greater use of combination treatment (70% versus 47%; relative risk 1.49; 95% confidence interval [CI] 1.30–1.72; \( P < 0.0001 \)); number needed to treat=4.4 (3.3–6.6) without differences in systolic blood pressure (−1.5 mmHg [95% CI −4.0 to 1.0]; \( P = 0.24 \)) or total cholesterol (0.08 mmol/L [95% CI −0.06 to 0.22]; \( P = 0.26 \)). At study end, 17% and 67% of participants in polypill and usual care groups, respectively, were taking atorvastatin or rosvastatin.” (ANZCTR 12608000583347)

We aim to explore the relevance of the polypill strategy for health providers and patients as a health service strategy to improve prescribing of indicated therapy and improve patient medication use. Understanding the mechanism of the polypill strategy from patients and providers perspectives will assist in translation of the polypill intervention to other contexts and so inform policy and practice in the area.

Methods

A predefined protocol for the overall process evaluation was used and had been published. Our methods are presented across key areas for reporting in qualitative research.

Research Team and Reflexivity

Study investigators involved in the design and implementation of KGAP developed the process evaluation protocol and interview guides. The interviews were conducted by a team of 7 researchers who varied in qualitative research experience and had diverse backgrounds (nursing, health economics, pharmacy, Indigenous health). Three were indigenous and 4 were nonindigenous researchers. Two of the interviewers were research coordinators and had existing relationships with several of the participants interviewed, but the other interviewers were not known to the participants before the interviews.

Study Design

Participants were recruited purposively based on maximum variation of specified variables, which could potentially affect participants’ views of a polypill-based strategy and with trial implementation. A sampling matrix was used with the following characteristics: for patients, these were location, age, sex, ethnicity, primary versus secondary CVD, and self-reported adherence at baseline; and for providers, location and profession. All health providers and patients were approached by a letter of invite detailing the study and purpose and a follow-up phone call by the project coordinator. All health providers approached agreed to participate, though 5 patients declined to be interviewed and 2 patients were unavailable. Written informed consent was obtained.

The interview guides covered the key domains about the polypill strategy in CVD management, patient satisfaction or problems with the polypill, issues regarding trial implementation, and...
translation of the polypill into clinical practice. Interview guides were iteratively revised to explore themes and issues emerging from earlier interviews. Interview guides are available as Data Supplements.

Ninety-four semistructured interviews were conducted at the end of KGAP with 47 providers (25 general practitioners [GPs], 13 pharmacists, 6 Aboriginal Health Workers, and 3 Chronic Care Nurses) and 47 patients in New South Wales, Queensland, and Victoria. Twenty-two and 25 patients were in the polypill arm and usual care arm, respectively. Twenty-one and 26 patients were in the primary and secondary prevention arm, respectively. There were 28 nonindigenous patients and 19 indigenous patients. Participant characteristics are included in Table in the Data Supplement.

Most interviews (ranging from 30 minutes to an hour) were conducted face to face either at home or at the health service and audio-recorded. Two interstate participants were unavailable at a time that coincided with travel to their health services. It was not feasible to schedule an additional visit because of time, interviewer availability, and cost. Instead, these 2 interviews were conducted by phone and audio-recorded. To ensure consistency, one researcher (L. Massi) was involved in most of the interviews. She conducted 42 alone and another 40 with another researcher. L. Massi was trained in qualitative research methods and coordinated the study. Preliminary thematic data analysis was conducted by L. Massi alongside the interviews and discussed with the research team. Thematic saturation was reached, and further interviews were conducted to ensure that we had gleaned perspectives from the different regions.

Analysis

Interviews were professionally transcribed and coded by 2 researchers (H. Liu and L. Massi) using NVivo 9 (QSR International, Melbourne, VIC) at the completion of the interviews. Using the constant comparative method, these researchers coded the same 12 transcripts independently through 3 iterative stages and developed an initial coding framework encompassing both patients’ and providers’ perspectives, allowing triangulation of findings within each code. Insights gained by the KGAP research team about the local setting and empirical results of the PRCTs were used to aid interpretation. H. Liu and L. Massi coded the remaining interviews equally, drawing up memos for each interview to provide additional context for others analyzing the data and recoded the original 12 interviews. Minor, iterative changes to code definitions were made. An audit trail was kept. For this article, all data assigned to codes relating to the polypill strategy in CVD management were analyzed by H. Liu and the Realist framework of context–mechanism–outcomes utilized to develop the themes (see Figure). Further description of the major codes and the coding framework are available as Data Supplements. The study was approved by 7 regional ethics committees.

Results

Three principle themes relating to the polypill as a health service strategy to improve CVD prevention in Australian primary care were derived (Table in the Data Supplement is available with additional quotes).

Overall Acceptability of the Polypill Strategy

Ease and Convenience

A key strength described by many patients and providers was that overall the polypill was liked and perceived as a beneficial strategy because of the ease and convenience of a single daily-dosing capsule. It was physically easier to take and to remember to take, which was highlighted by some providers and patients as especially important for the elderly and for those with stressful and competing life priorities.

A few providers assumed that the polypill would increase adherence because long-term adherence to preventative medication was challenging for their patients. An indigenous patient described how the polypill reduced her psychological pill burden:

… taking so many individual tablets became stressful, it’s like you knew what was happening like this organ and that organ is not working but with the polypill, because it’s all in one and you’re not having these different things laid out before your eyes. It was easy. (Patient 31, remote IHS)
Cost Savings

The polypill strategy was a pragmatic trial, which aimed to mimic real-world cost impacts on participants. In the Australian context, where medications could be subsidized through the Pharmaceutical Benefits Scheme (PBS), nonconcession card holders would pay full copayments for prescriptions (≈$AUD30), whereas concession card holders would pay subsidized copayments of $AUDS.60 for each prescription. For these groups, there was a potential 4-fold cost advantage of the polypill. For indigenous participants who were eligible for complete medication subsidization through a government scheme newly introduced during the PRCT, there was no cost advantage of the polypill because treatment in both arms was subsequently free. Thus, depending on individual circumstance, the savings varied for the patients.

When I was working [all] my medications … used to cost me almost $320 a month at the full price. Individually some of them are very expensive; you might be paying $20 or $25 for each one. Now [on pension rates], it is $5.80 for the combined [polypill]. (Patient 17, rural GP clinic)

The cost of medications does not impact me because, I’m working, and I’ve got a good job. (Patient 38, regional GP clinic)

Before I went on the polypill it was so hard. It’s the affordability, and taking all these different tablets at different times, whereas now it’s one tablet, and it’s free, so you can’t get it any better than that. (Indigenous patient 13, IHS)

Most of the providers recognized that the polypill would help improve their patients’ adherence to CVD medications because of ease, convenience, and cost-savings of the polypill.

A GP described the advantages of the polypill for his patients and in starting medications:

Taking one pill instead of four is excellent and improves compliance with patients; there is a cost factor that is an advantage. There is a simplicity factor – it’s easier to start someone early on, on a four-medication thing if they need it. If someone sort of never comes in and is poorly compliant and for months or years they’ve sort of had little warning signs that they really need something done but they don’t really do it, the polypill does make it possible to fairly easily say, ‘let’s take this pill instead of this pill, it’s just that this pill contains four medications.’ (GP 27, urban IHS)

The perceived advantages of the strategy as described by many of the providers may explain the difference in the prescription of antiplatelet, statin, and at least 2 blood pressure lowering agents which at baseline percentage was 50% and increased to 79% in the polypill arm and only 52% in the usual care arm.

Adherence Depends on Other Factors

However, despite many patients describing how and why the polypill could improve medication use, other factors were also described by the patients as being key to their adherence. Patients indicated that their adherence behavior was determined by intrinsic factors, such as establishing routine medication regimens, their sense of well-being, and their understanding of medications, aided by external factors, such as the perceived quality and accessibility of their healthcare, family, and community support, respectful patient–provider relationships, and financial assistance from the government.

Examples of quotes illustrating these factors include:

Because the one [reason] that keeps my heart going, well, because I’ve got my little fellow now. I want to try and stay here long as I can for him. (Patient 22, regional GP clinic)

I mean when you see the people that are dying around you … the same age as you and even younger, it’s all to do with health that they died not taking medication. (Patient 4, urban IHS)

Keep the medication affordable; cost of living is high enough now…especially for black people because for black people, diabetes, sugar and all those type of things, is something that has impacted on us since colonisation of this country and the introduction of processed foods. So we need to have medication available to us to keep us living a longer life than what we’re currently living and if medication is the only way to keep us going then we need to be able to afford to have it. (Patient 10, urban IHS)

Patients also described initiatives, such as having dose administration pack, removed the hassle of carrying many medications, and served as a reminder to take their medications. Similarly, many providers perceived intrinsic and extrinsic factors affected their patients’ medication use.

It’s very hard, we’ve done motivational training [in regards to adherence] and the Division [of GP’s] has tried all sorts of things to help these people and they’re just not interested. They have lives often with so many complexities which they can’t manage. (GP 36, regional GP clinic)

Clearly the evidence around the world is that the primary care practitioner/patient relationship is the magic ingredient in the health system. There’s continuity and there’s trust. You get better outcomes and part of that is that people are more willing to commit to treatment plans. I think the General Practitioner’s role is key in promoting adherence. (GP 1, rural GP clinic)

Many providers indicated that the perceived potential impact of the polypill strategy in improving their patients’ medication use depended on existing adherence behavior. For example, though pharmacist 42 (remote IHS-related pharmacy) talked about how if pill burden was a key barrier then the polypill would be ideal, another pharmacist described a limited impact of the polypill strategy if patients were already adherent and used dose administration devices:

People’s compliance is pretty high. So whether they have good result or not, because they are using a [dose administration pack], they pop it anyway. So if they have four pills, all separate, or one pill in poly-pills, it’s no difference. (Pharmacist 21, urban IHS-related pharmacy)
Polypill Strategy in Patient Management

Limitations of a Fixed Dose Combination

Some providers described certain limitations of the polypill strategy in patient management. They commented on the inflexibility of a fixed dose combination and on the complexity in identifying which component of the polypill caused any reported side effect.

“I think the Polypill is a good idea in principle but it also showed me how complicated it is to give somebody a pill with four components. One of the biggest parts of my work is dealing with adverse drug reactions and if you give a person one medication there’s a pretty good chance they’re going to get an adverse reaction. Now it may be a minor one, may not be, if you give them four, that’s a lot more chances. And then teasing out which one is difficult. (GP 10, urban GP clinic)”

At some sites, providers described patients on the trial with complex medical problems that in hindsight were not sufficiently stable for the polypill.

“I was surprised with some of the patients whom others had been happy to put on it because when we looked at the problems that some [patients] had, I thought, well I wouldn’t have put that person in the trial, in the first place (because) they were quite complicated and there will be potential risks of having some problems on the polypill. (GP 36, regional GP clinic)”

Some providers found that the polypill formulations used in the trial contained inadequate dosages for their patients, expressing an inclination to discontinue its use if additional medications were needed because the advantage of a one daily-dosing pill was lost.

Adequacy of the Polypill Components

The therapeutic efficacy of the generic components within the polypill was discussed by many of the providers. There were 2 perspectives: some GPs questioned whether these particular polypill formulations would represent best practice, given the perceived superiority of some of the newer on-patent medications available. Conversely, some providers preferred the use of off-patent medications contained in the polypill because of the cost-savings and the greater evidence-base of these older medications. A GP gave the following opinion of the on-patent medications compared with the older generics:

“So much of the PBS is bound up with cardiovascular management. I have a personal belief that we spend far too much on the PBS. There are far too many medications that are not generic and we seem to want to have the most expensive and I personally don’t believe in that. I think people are prepared to live their lives as they wish and [some] smoke and drink. We do our best and we assume that the medication is, a hundred per cent, is all the treatment, which it’s not. So I don’t believe they have to have Rolls Royce medications when they lead a beat up Hyundai Lifestyle. What they need is to actually take the medications regularly, understand what they’re for... I’d much rather go with a lot more evidence-based cheaper medications and getting people to take them. (GP 39, remote IHS)”

Some GPs also expressed an uncertainty about the individual components. Several providers were uncertain about the use of aspirin for nondiabetic patients without established CVD. Some of the GPs and the patients’ cardiologists preferred to prescribe the newer statins if possible. This was also reflected in the PRCT’s data, which showed that at the end of the study, 17% and 67% of participants in polypill and usual care groups, respectively, were taking atorvastatin or rosuvastatin.

“I think that there was one local cardiologist who wasn’t at all supportive of the polypill .... And this particular cardiologist also tended to use the top end dose of statins when he’d seen a patient, so that had the potential to raise an issue for a patient who we would then have to prescribe polypill plus an additional statin to keep them on the same dose as the cardiologist... I’m not actually convinced that the patients all needed to be on that dose. (GP 25, urban IHS)”

These providers’ perspectives about limitations of a fixed dose combination and questions regarding the adequacy of the polypill components offer possible explanations of why 28% of patients who were randomized to the polypill stopped it at some stage with around half of these discontinuations being because of prescribing and, thus apparently, were provider-initiated.

Future Combinations Would be Beneficial

Many providers and patients believed the above mentioned limitations could be overcome by having other polypills with different drug combinations. Some providers also stated a combination pill could be formulated for other diseases like diabetes mellitus, as in the following quote:

“Once the general principle of a cardiac medication that’s polyvalent is established then there ought to be some flexibility as to what components might be added, with the advantage of future research. (GP 23, urban IHS)”

Who Could it be Suitable for?

High-Risk Primary Prevention Patients

Many providers were of the belief that the polypill formulations used in the study were inappropriate for some secondary prevention patients because of the low and inflexible dosing. Rather, its niche was in high-risk primary prevention patients who were stable medically.

“Using a generalised polypill with lower doses where you have a person who hasn’t got the cardiovascular disease but has cardiovascular risk would be good just to help them from developing full-on cardiovascular disease. I think there’s a role there - where there might be the one blood pressure tablet … because they might have had minor hypertension and putting a statin in there with aspirin just keeps everything functioning well and stops them getting established...”
cardiovascular disease. Whether it’s got a role in the patient who already has cardiovascular disease, I’m not sure because you can’t alternate the doses the way you want. (Pharmacist 7, urban IHS)

This theme supports the trial finding of the polypill-based strategy, resulting in a proportionately greater improvement in combination treatment use among high-risk primary prevention patients, though this improvement was also significant in patients with established disease.

**Strategy to Address CVD Burden in Indigenous Patients**

Although the acceptability of the polypill strategy on improving adherence was reported by both patients and providers in IHSs and private clinics, a strong finding was that there could be particular advantages for indigenous patients. A GP thought the polypill could be an effective strategy to reduce the CVD burden in his community:

> Being an Aboriginal doctor I see the burden of disease especially in cardiovascular health…. The youngest fellow we’ve had coming in here is 28 having a heart attack. So we see heart disease early and it’s not uncommon for some of our patients to have heart attacks in their 30s, 40s and 50s. So I think we need some other strategy to help decrease that risk and that’s where I’ve seen the place for the polypill and it’d be interesting to see what results come out of it. (GP 28, urban IHS)

A GP (Provider 43, remote IHS) described the usually lengthy process of starting medications in indigenous patients and how the polypill could be used to expedite this process. Moreover, by not having a pharmacist provide medications in a medication dose aid might mean increased ownership of health for his patients on the polypill. An indigenous patient thought the polypill would be a way to bridge the health literacy gap:

> It would be a good thing … for a lot of our people … if they’ve got to take about half a dozen tablets or four tablets you know they might get confused. Some of our people you can’t read much to know what tablets to take. They just take them… [They] don’t know what they’re taking it for. I reckon it’s a good idea if they’ve got the polypill [which] is all in the one. (Indigenous patient 43, remote IHS)

Several GPs at some IHSs thought the polypill strategy complemented their services’ chronic disease model of care, updated them on their CVD guidelines, and encouraged them to use the CVD absolute risk calculation in their patient management. Provider 20 (pharmacist, urban IHS) thought the polypill strategy worked synergistically with the GP’s education of patients and the pharmacists’ provision of the dose administration aid to improve patients’ adherence.

It seemed that the polypill strategy could potentially be beneficial for the indigenous population, given the high disease burden and the complexities associated with taking multiple medications. It was viewed as an acceptable strategy by patients and providers for high-risk, medically stable patients. Many IHS providers thought the polypill strategy could be an effective component of CVD care that could be integrated into strategies that address other factors, such as accessible care, health promotion, and social determinants. Indeed, the PRCT subgroup analysis showed that there was a significant improvement in medication use among the indigenous patients randomized to the polypill strategy.

**Discussion**

The polypill strategy is relevant to patients’ and providers’ needs as an acceptable health service strategy to improve CVD prevention in Australian primary healthcare. Using the Realist framework, the effectiveness of the polypill strategy was dependent on whether the health provider felt that the polypill components were adequate for the management of individual patients’ CVD, and would encourage patient’s adherence because of its ease and convenience, and cost savings for the patient. However, the sustainability and impact of the polypill strategy in improving adherence depended on other patient factors, such as affordability of medications, level of health literacy, compatibility with existing adherence strategies, sense of well-being, patient–provider relationship, access to quality care, and disease stability and severity. The main limitation of the strategy was the inflexibility in dosing, but this was viewed as a shortcoming that could be addressed with introduction of a wider range of combinations. In its current formulations, many of the providers in this study deemed it to be particularly suited to high-risk primary prevention patients and some indigenous populations in Australia.

Our study confirms some findings of other qualitative studies which showed a growing acceptance of prescribing the polypill for primary and secondary prevention, provided there is evidence of effectiveness and cost benefits. However, our study also highlighted overall patient acceptability of the polypill strategy and a key recommendation by providers to improve the flexibility of the polypill strategy in meeting the varied needs of patients by introducing more formulations. Using qualitative research alongside a PRCT enabled us to better appreciate the role of the polypill strategy in addressing inequity within contextual factors of Australian primary healthcare, such as high CVD burden within indigenous communities, existing costs of medications, and concurrent government policies for medication subsidies.

This study was limited in that it was an in-depth exploration of issues from a sample that was not necessarily representative of all participants and providers in the trial. Fewer interviews were done in remote sites, and staff who had left the service or participants who had withdrawn by the end of the study would not have been interviewed. Other limitations of our study include having 2 interviews done over the phone in comparison to face to face, varying level of experience of qualitative research among the study team and achieving only partial member checking during a presentation of preliminary findings to a subset of providers.

Though the KGAP trial showed that there was improved adherence in the polypill arm, patients’ adherence in both arms of the study progressively declined over time, which is consistent with the literature. Thus, the question remains as to how to best use the polypill strategy to improve sustained medication adherence. A method to characterize behavior
change interventions was proposed by Michie et al through the use of a behavior change wheel, which comprises a behavior system at the hub, encircled by 9 intervention functions aimed at addressing the deficits in capability, motivation, and opportunity and then by 7 policy categories to enable the interventions to occur. Applying Michie’s behavior change wheel to our results, it seems that the polypill strategy has the intervention functions of enablement and incentivization; to effect behavior change, but perhaps other intervention strategies and policies are needed for sustained change. Multifaceted approaches to improve adherence have been trialled internationally. In Australian primary health care, a quality improvement intervention with pharmacists-led education to improve health literacy and electronic decision support for the prescribing of preventative medications has been shown to be effective. Our study findings suggest that the polypill strategy could potentially be used successfully and synergistically with similar health service strategies to improve medication persistence in this setting.

The polypill strategy is increasingly being recognized as a part of a solution for improving global CVD prevention, with a growing body of evidence showing effectiveness in improving provider prescribing and patient adherence to indicated CVD medications. The economic evaluation conducted with the KGAP trial and a cost-effectiveness study of a multidrug regimen (similar to the polypill components) in a lower middle income setting provide promising evidence that the polypill strategy could reduce the high global economic burden of CVD, given the availability of the inexpensive yet effective drugs. As more CVD medications come off patent, our findings imply a key challenge would be to have different polypill versions made available as an affordable and attractive health service strategy for both high-income and lower middle-income countries. However, barriers to the implementation of the polypill strategy include the manufacture of the polypill as a viable business for pharmaceutical companies, despite its huge public health potential and having supportive legislation and policy changes. As such, the amalgamation of evidence from international trials combined with further research in cost effectiveness and acceptability of the strategy in different contexts will determine the feasibility and policy significance of the polypill strategy in improving CVD prevention worldwide.

Acknowledgments
We thank Deborah Blair, Barry Fewquandie, and Chris Lawrence for assisting in the interviews. We also acknowledge staff and patients from participating general practices and IHSs who gave generously of their time in providing us their perspectives. An extensive team from participating general practices and IHSs who gave generously of their time in providing us their perspectives.

Sources of Funding
The study was funded by the National Health and Medical Research Council (NHMRC) of Australia (App: 1004623). A. Cass and A. Patel are funded by Senior Research Fellowships from the NHMRC. S. Jan is funded by an NHMRC Career Development Award. T. Laba is funded by an NHMRC Scholarship and NHMRC Capacity Building Grant (57132). A.M. Eades is funded by an NHMRC Scholarship (1056434). J. Redfern is funded by a NHMRC-National Heart Foundation Health Professional Fellowship. The funder and Dr Reddy’s Laboratories (provided polypills free of charge for the clinical trial) had no role in the study design, data collection and analysis, decision to publish, or preparation of the article.

Disclosures
The George Institute for Global Health recently secured an exclusive global license for the polypills evaluated in the KGAP trial, following a decision by Dr Reddy’s Laboratories Ltd not to proceed with taking the products to market because of existing regulatory requirements; apart from the declared, there are no other relationships or activities that could seem to have influenced the submitted work.

References
Patients' and Providers' Perspectives of a Polypill Strategy to Improve Cardiovascular Prevention in Australian Primary Health Care: A Qualitative Study Set Within a Pragmatic Randomized, Controlled Trial

Circ Cardiovasc Qual Outcomes. 2015;8:301-308; originally published online May 5, 2015; doi: 10.1161/CIRCOUTCOMES.115.001483
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/8/3/301

Data Supplement (unedited) at:
http://circoutcomes.ahajournals.org/content/suppl/2015/05/05/CIRCOUTCOMES.115.001483.DC1
http://circoutcomes.ahajournals.org/content/suppl/2015/05/06/CIRCOUTCOMES.115.001483.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online at:
http://circoutcomes.ahajournals.org/subscriptions/
RE: CIRCCO/2014/001033 Revision of ‘Understanding adherence to a cardiovascular polypill strategy: a qualitative study set within a pragmatic clinical trial.’

Responses to Reviewers’ comments
(Note: Reference to the amendments are highlighted on the tracked changes manuscript)

Reviewer #1:
1) This is an interesting paper that uses qualitative methods to help assess the appropriateness of using polypills in CVD patients. It is helpful to represent provider and patient perspectives regarding this subject and interviews is a good method to use to elicit these views. I make the following suggestions to improve the paper. It would be helpful for readers to have the list of questions asked of providers and patients.

Response: Thank you for your suggestion. The following amendment has been made in the methods to outline the key domains of questions within the interview guide and the interview guides for health providers and patients are provided as online supplements.

Amendments are made on page R7 lines 137-141: The interview guides covered the key domains about the polypill strategy in CVD management, patient satisfaction or problems with the polypill, issues regarding trial implementation, and translation of the polypill into clinical practice. Interview guides were iteratively revised to explore themes and issues emerging from earlier interviews. Interview guides are available as online data supplements.

2) P5: please indicate what is meant by logistical reasons telephone interviews were needed.
Distance, costs, other?

Response: This detail has been added in the manuscript.

Amendments made in page R8, lines 150-153: Two interstate participants were unavailable at a time that coincided with travel to their health services. It was not feasible to schedule an additional visit due to time, interviewer availability and cost. Instead, these two interviews were conducted by phone and audio-recorded.

3) It would strengthen the methods section to have more information about how the interviews were conducted and analyzed. Specifically, did LM and HL conduct all the interviews? How many were done by only 1 interviewer? How many with a second person observing? I assume interviews were audio-recorded since transcripts were coded (is that right?). If the coding scheme was modified iteratively, were the originally coded transcripts re-coded to reflect the new or altered codes? Please provide examples of codes. Who determined the themes? How were disagreements about codes and/or themes reconciled among team members? Was an audit trail kept of analytic decisions?

Response: Thank you for highlighting areas for improvement within the methods section. We have elaborated on the methods and changes have been made in the structure of the methods according to the consolidated criteria for reporting of qualitative studies developed by Tong et al from a review of qualitative studies and guidelines. (1) Additionally Figure 1 outlines the Context-Mechanism-Outcomes framework and how the codes were grouped to develop the themes in the process of analysis. A description of the major codes as a table is available as an online data supplement.

Relevant amendments have been made on page R7, line 119 through to page R12, line 230.

4) Information about the recruitment of participants would be more appropriate in the methods rather than results section.

Response: Thank you for this suggestion, this information has been moved to the methods section page R8 lines 142-148:

94 semi-structured interviews were conducted at the end of KGAP with 47 providers (25 General Practitioners (GPs), 13 pharmacists, 6 Aboriginal Health Workers (AHW) and 3 Chronic Care Nurses) and 47 patients in New South Wales, Queensland and Victoria. Twenty-two and 25 patients were in the polypill arm and usual care arm respectively. Twenty-one and 26 patients were in the primary and secondary prevention arm respectively. There were 28 non-Indigenous patients and 19 Indigenous patients. Participant characteristics are included in an online supplementary table.
5) It is unclear how the patients and providers were actually recruited. Please describe if this was a convenience snowball sample or what methods of recruitment were used. Who was considered appropriate to recruit? It is important to clarify some parameters of inclusion.

Response: Amendments have been made on page R7 lines 128-132 in regards to sampling: Participants were recruited purposively based on maximum variation of specified variables which could potentially impact upon participants’ views of a polypill-based strategy and with trial implementation. A sampling matrix was used with the following characteristics: for patients, these were location, age, gender, ethnicity, primary versus secondary CVD, and self-reported adherence at baseline; and for providers, location and profession.

6) Similarly, it’s important to include how many providers and patients refused to participate and their reasons for declining participation.

Response: Reasons for declining participation included participants not being available but otherwise further information was not collected across all sites.

Amendments made on page R7 line 132-135: All health providers and patients were approached by a letter of invite detailing the study and purpose, and a follow up phone call by the project coordinator (LM). All health providers approached agreed to participate though 5 patients declined to be interviewed and two patients were unavailable.

7) Regarding the identification of themes and subthemes, it would be helpful to have a table to list these. It is difficult to relate the text to the figure, and the connections between these is not apparent.

Response: Thank you for this suggestion, the codes and themes are listed in Figure 1 and a description of the major relevant codes and the coding framework figure are included as online data supplements instead.

Amendment made to include Figure 1: Themes and codes within the Realist Framework (Context, Mechanism and Outcome)
8) It is useful to write themes as sentences so as to express a complete thought. The "adherence depends on other factors" theme is more meaningful expressed as a sentence than a theme titled "polypill components," for example.

Response: The themes have been altered to reflect this. Please see page R18 line 373, page R20 line 412, page R21 line 437.

9) Under ease and convenience, we are told that providers "assume" a variety of benefits but there are no quotes to represent these statements.

Response: This statement was a summary of a few providers' perspectives and was not quoted due to word limit constraints.

However, a quote from a provider which represented many providers' views of the main benefits of the polypill strategy is presented on page R14 lines 275-282:

Taking one pill instead of four is excellent and improves compliance with patients; there is a cost factor that is an advantage. There is a simplicity factor – it's easier to start someone
early on, on a four-medication thing if they need it. If someone sort of never comes in and is poorly compliant and for months or years they’ve sort of had little warning signs that they really need something done but they don’t really do it, the polypill does make it possible to fairly easily say, ‘let’s take this pill instead of this pill, it’s just that this pill contains four medications.’ (GP 27, urban IHS)

10) It would be good to see patient quotes to illustrate the “adherence depends on other factors” theme. The entire theme is from the point of view of providers; the patient perspective should be included here.

Response: Thank you for highlighting this deficit in the reporting of our findings. Quotes have been included in the text and in an online data supplementary table of more quotes to illustrate the findings.

Amendments made on page R15, lines 297-310:

Examples of quotes illustrating these factors include:

Because the one [reason] that keeps my heart going, well, because I’ve got my little fellow now. I want to try and stay here long as I can for him. (Patient 22, regional GP clinic)

I mean when you see the people that are dying around you ... the same age as you and even younger, it’s all to do with health that they died not taking medication. (Patient 4, urban IHS)

Keep the medication affordable; cost of living is high enough now...especially for black people because for black people, diabetes, sugar and all those type of things, is something that has impacted on us since colonisation of this country and the introduction of processed foods. So we need to have medication available to us to keep us living a longer life than what we’re currently living and if medication is the only way to keep us going then we need to be able to afford to have it. (Patient 10, urban IHS)

11) Table 3 could use more explanation in the text. The authors might consider a figure or flow chart to better illustrate the content of this table, which is difficult to follow.

Response: Thank you for this suggestion. A flowchart highlighting the themes is shown in Figure 1 instead of table 3, and its’ explanation is provided as a summary in the discussion.

Amendments made on page R25, lines 522-534:
The polypill strategy is relevant to patients and providers’ needs as an acceptable health service strategy to improve CVD prevention in Australian primary health care. Using the Realist framework, the effectiveness of the polypill strategy was dependent on whether the health provider felt that the polypill components were adequate for the management of individual patients’ CVD, and would encourage patient’s adherence due to its ease and convenience, and cost savings for the patient. However, the sustainability and impact of the polypill strategy in improving adherence depended on other patient factors such as affordability of medications, level of health literacy, compatibility with existing adherence strategies, sense of wellbeing, patient-provider relationship, access to quality care, and disease stability and severity. The main limitation of the strategy was the inflexibility in dosing but this was viewed as a shortcoming that could be addressed with introduction of a wider range of combinations. In its current formulations, many of the providers in this study deemed it to be particularly suited to high-risk primary prevention patients and some Indigenous populations in Australia.

12) The discussion would benefit from the addition of considerations about future directions and implications.

Response: We greatly appreciate this feedback and changes have been made to the discussion in regards to the future directions of using a polypill based strategy for CVD prevention.

Amendments made in pages R28, lines 590-622: (abbreviated here)

Though the KGAP trial showed that there was improved adherence in the polypill arm; patients’ adherence in both arms of the study progressively declined over time which is consistent with the literature. (2-4) Thus, the question remains as to how to best use the polypill strategy to improve sustained medication adherence... As more CVD medications come off patent, our findings imply a key challenge would be to have different polypill versions made available as an affordable and attractive health service strategy for both high income and lower middle income countries. However, barriers to the implementation of the polypill strategy include the manufacture of the polypill as a viable business for pharmaceutical companies despite its huge public health potential, and having supportive legislation and policy changes. As such, the amalgamation of evidence from international trials, combined with further research in cost effectiveness and acceptability of the strategy in different contexts will determine the feasibility and policy significance of the polypill strategy in improving CVD prevention worldwide.
Reviewer #2:

1) This review does not address the larger question of relevance and contribution to a defined gap in the literature, and focuses on the methodology and findings as reported. On this point, however, there is a substantial literature on medication adherence in high risk patients relevant to this study that could be distilled and synthesized more effectively in order to place the findings in context and to strengthen the case for its particular contribution to the literature.

The use of qual methods within RCTs is gaining traction and has tremendous potential - see Lewin et al in BMJ on this (should be cited to point readers to this approach). The application of this method in the current study is appropriate and well conceived. Yet there are important limitations and questions that need to be addressed.

Response: Thank you for your suggestion and for directing us to this resource. The introduction and sections of the discussion has been amended to include this information to frame our findings.

The following paragraph has been added to the introduction page R4 lines 62-68:

However, whether this promising result is generalizable and can be successfully implemented in health services outside of trial settings depends partly upon whether the polypill strategy will be well received by health providers, and importantly to patients. This can be addressed by qualitative research conducted alongside trials exploring relevant stakeholders’ perspectives. (5-7) The use of the Realist framework has been successfully used in process evaluations as a theoretical basis for identifying potential causal mechanisms of how an intervention works for whom, under what contexts and thus fosters uptake of research based knowledge into practice. (8-12)

In the discussion, pages R26, line 545-554 reinforce the importance of using qualitative methods with RCTs:

Using qualitative research alongside a PRCT enabled us to better appreciate the role of the polypill strategy in addressing inequity within contextual factors of Australian primary health care such as high CVD burden within Indigenous communities, existing costs of medications and concurrent government policies for medication subsidies.

2) Additional information and clarification is needed as to the use of standard qualitative research principles and practices, including: a) rationale and consequences of the sampling approach as described, b) aspects of the data collection process, and c) the analytic approach.

Sample included only those who were actively enrolled/had completed the study, and had
‘successful adherence’ as reported in the findings. Please provide rationale and note potential biases. Was there consideration of a purposeful selection approach with attention to characteristics that have been shown to influence medication adherence (age, education)?

Please elaborate on criteria for determining that saturation was achieved and describe more clearly the timing of the coding. Was it interspersed with interviewing?

Response: Participants were recruited purposively using a sampling matrix of maximum variation of characteristics which may affect patients and health providers’ views of the polypill as a health service strategy, such as reported baseline adherence of patients. Interviews were conducted at the end of study so as not to bias the participants about the intervention through the interviews. However, this does limit the study as we did not obtain views from patients who may not have completed the study. LM did preliminary thematic data analysis alongside the conduct of interviews and discussed her findings with the study investigators and interview team. Saturation was achieved when no new preliminary major codes were created. However, further interviews were conducted to ensure that perspectives from the different sites were obtained eg. remote versus urban sites.

As per response reviewer comment 3, amendments to the methods to provide more detail and to structure it according to reporting of qualitative research criteria set out by Tong et al.(1) have been made. Please see page R8 line 154-158, and page R11, line 219.

3) Data collection: please note the background and experience of those conducting interviews, describe why some were in phone and others person and note possible limitations of mixing these modalities of data collection.

Response: Thank you for this suggestion. The background of the research team and a description of why there were two phone interviews have added to the methods on page R7, lines 120-126:

Study investigators involved in the design and implementation of Kanyini GAP developed the process evaluation protocol and interview guides. The interviews were conducted by a team of seven researchers. The team varied in qualitative research experience and had diverse backgrounds (nursing, health economics, pharmacy, Indigenous health). Three were Indigenous and 4 were non-Indigenous researchers. Two of the interviewers were research coordinators and had existing relationships with several of the participants interviewed but the other interviewers were not known to the participants prior to the interviews.
The limitation of mixing these modalities of data is added in the discussion page R28, line 589:

Other limitations of our study include having two interviews done over the phone in comparison to face to face...

4) Please include the final version of the interview guide.

Response: Attached as online data supplement.

5) Participant validation with only subset of providers seems problematic.

Response: Thank you for highlighting this issue and it is a limitation of the study. However due to the close communication and network among the health providers, there was informal feedback to the research staff about the polypill strategy and these insights and contexts were used in the analysis of the data. Nevertheless, this issue is now noted as a limitation of the study in the discussion page R28, lines 586-589:

Other limitations of our study include having two interviews done over the phone in comparison to face to face, varying level of experience of qualitative research among the study team and achieving only partial member checking during a presentation of preliminary findings to a subset of providers.

6) Data analysis- Was there any attempt to do comparative analyses between provider and patient views? Discordance? And if so how?

Response: There was an attempt to do comparative analysis between provider and patient views. HL and LM used grounded theory and inductive analysis to code the same 12 interviews (with even numbers of patients and providers) thus analysing the data through individual cases. (13) Using these codes a coding framework was developed to highlight relationships between codes. Subsequently, comparative and cross case analysis was done by reviewing all data coded to a major code by both patients and providers, looking at different views between providers and patients and checking especially for the ‘deviant’ case. This process provided greater insight into the development of the themes. For the purposes of this paper, the author HL focused on codes relating to the relevance of the polypill strategy in CVD prevention and LM reviewed other codes such as
general adherence, and they had regular in depth discussions as they established emerging themes. This provided researcher triangulation and increased the reliability and validity of the study. (13)

The methods section has now been amended to include this information briefly. See page R11, lines 214-219:

Interviews were professionally transcribed and coded by two researchers (HL and LM) using NVivo 9 (QSR International, Melbourne, VIC) at the completion of the interviews. Using the constant comparative method (7), these researchers coded the same 12 transcripts independently through 3 iterative stages and developed an initial coding framework encompassing both patients and providers perspectives; allowing triangulation of our findings within each code.

7) It is not at all clear how the coding framework was operationalized to generate the recurrent themes as reported. Much more is needed on this, including the code structure.

Response: Codes and derived themes are depicted in Figure 1 to illustrate the use of the Realist framework in developing the themes. A table with a description of the major codes is also included as an online data appendix.

8) More information about the triangulation across interviews and quantitative findings from the RCT would strengthen the paper.

Response: Thank you for this comment, the primary outcomes of quantitative findings from the PRCT have been presented in the introduction, and relevant quantitative findings have been included in the results.

Amendments made on-

- Page R6 lines 102-110: Primary outcomes were measured by self-reported medication use and changes in biological markers of changes in systolic blood pressure and total cholesterol. Results showed that "After a median of 18 months, the polypill-based strategy was associated with greater use of combination treatment (70% vs. 47%; relative risk 1.49, (95% confidence interval (CI) 1.30 to 1.72) p<0.0001; number needed to treat = 4.4 (3.3 to 6.6)) without differences in systolic blood pressure (-1.5 mmHg (95% CI -4.0 to 1.0) p = 0.24) or total cholesterol (0.08 mmol/l (95% CI -0.06 to 0.22) p = 0.26). At study end, 17% and 67% of
participants in polypill and usual care groups, respectively, were taking atorvastatin or rosuvastatin.” (ANZCTR 1260800583347)(14)

- Page R14 line 283-286: The perceived advantages of the strategy as described by many of the providers may explain the difference in the prescription of antiplatelet, statin and at least two blood pressure lowering agents which at baseline percentage was 50% and increased to 79% in the polypill arm and only 52% in the usual care arm.

- Page R19 lines 396-398: This was also reflected in the PRCT’s data which showed that at the end of the study, 17% and 67% of participants in polypill and usual care groups, respectively, were taking atorvastatin or rosuvastatin.

- Page R20 lines 408-413: These providers’ perspectives about the limitations of a fixed dose combination, and questions regarding the adequacy of the polypill components offer possible explanations of why 28% of patients who were randomised to the polypill stopped it at some stage with around half of these discontinuations being due to prescribing and thus apparently, were provider initiated.

- Page R21 lines 433-435: This theme supports the trial finding of the polypill-based strategy resulting in a proportionately greater improvement in combination treatment use among high-risk primary prevention patients, though this improvement was also significant in patients with established disease.

- Page R23 lines 478-480: Indeed, the PRCT subgroup analysis showed that there was a significantly improvement in medication use among the Indigenous patients randomised to the polypill strategy.

The coding framework was developed from both patients and providers interviews so as to be able to triangulate our findings within the same codes and themes. See reviewer 2 response 7. This detail is now added in our methods. Please see page R11 lines 218.

9) More citations for analysis and methods in general are needed.

Response: The methods section has been rewritten to reflect this. Please see page R7 lines 118,132, page R11 lines 221,223,228 and page R12 line 228.

10) Findings- The findings are well written and interesting to read; however, as presented the uniquely novel insights are not clear, nor are they positioned relative to what is known about medication adherence in this context.
Response: The introduction and discussion have been amended to highlight the question about the role of the polypill strategy in improving prescribing of indicated therapy, and patient adherence to CVD medications.

- Amendments on page R3, lines 53-61: The reasons for non-adherence fit into well-recognised categories - health system, condition, patient, therapy and socioeconomic. (15, 16) A review of strategies targeting CVD medication non-adherence in disadvantaged populations found that interventions directed at patients and providers simultaneously showed statistically significant improvements in relative adherence. (17) Cardiovascular polypills which are fixed dose combinations of frequently indicated cardiovascular medications for high risk primary prevention and secondary prevention have been trialled internationally to improve provider prescribing and patient medication use. Encouragingly, recent results from randomised controlled trials have shown effectiveness in improving adherence. (14, 18, 19)

- Amendments in discussion on page R28, lines 590-606: Though the KGAP trial showed that there was improved adherence in the polypill arm; patients’ adherence in both arms of the study progressively declined over time which is consistent with the literature. (2-4) Thus, the question remains as to how to best use the polypill strategy to improve sustained medication adherence. A method to characterise behaviour change interventions was proposed by Michie et. al. through the use of a behaviour change wheel which comprises of a ‘behaviour system’ at the hub, encircled by nine intervention functions aimed at addressing the deficits in capability, motivation and opportunity, and then by seven policy categories to enable the interventions to occur. (20) Applying Michie’s behaviour change wheel to our results, it seems that the polypill strategy has the intervention functions of ‘enablement’, and ‘incentivisation’ to effect behaviour change but perhaps other intervention strategies and policies are needed for sustained change. Multifaceted approaches to improve adherence have been being trialled internationally. (16, 21, 22) In Australian primary health care, a quality improvement intervention with pharmacists led education to improve health literacy and electronic decision support for the prescribing of preventative medications has been shown to be effective. (21) Our study findings suggest that the polypill strategy could potentially be used successfully and synergistically with similar health service strategies to improve medication persistence in this setting.
Reviewer #3:

1) Conducting qualitative research of this sort is very important. However, the focus on the design of a specific trial, rather than the perceived barriers to use and adherence, limits the generalizability and impact of this contribution significantly.

Response: We appreciate this feedback. The original purpose of the process evaluation was to reflect upon issues of trial implementation and to assess the relevance of the polypill strategy to patients and providers to aid implementation into practice. As such, in response to the feedback, the focus of the paper has been narrowed to the perceived role of the polypill strategy in meeting the needs of patients and providers to allow for greater generalizability through using the Realist framework of what works, how and for whom.

Amendments on page R4 lines 62-69:

However, whether this promising result is generalizable and can be successfully implemented in health services outside of trial settings depends partly upon whether the polypill strategy will be well received by health providers, and importantly to patients. This can be addressed by qualitative research conducted alongside trials exploring relevant stakeholders’ perspectives. (5-7) The use of the Realist framework has been successfully used in process evaluations as a theoretical basis for identifying potential causal mechanisms of how an intervention works for whom, under what contexts and thus fosters uptake of research based knowledge into practice. (8-12)

2) The number of interviews conducted is truly impressive. Would be good to emphasize that saturation was achieved, and also to indicate how many additional interviews were conducted to confirm no new themes emerged.

Response: This detail is now added into the methods. Please see page R8, lines 155-158:

Preliminary thematic data analysis was conducted by LM alongside the interviews and discussed with the research team. Thematic saturation was reached and further interviews were conducted to ensure that we had gleaned perspectives from the different regions.

3) Would also be helpful to indicate the numbers of each type of healthcare provider interviewed. Currently it is only in the table, but would be good to include in the Results section as well.
Response: The numbers of each type of healthcare provider interviewed have been included in the text within the methods section.

Please see page R8, lines 142-148:

94 semi-structured interviews were conducted at the end of KGAP with 47 providers (25 General Practitioners (GPs), 13 pharmacists, 6 Aboriginal Health Workers (AHW) and 3 Chronic Care Nurses) and 47 patients in New South Wales, Queensland and Victoria. Twenty-two and 25 patients were in the polypill arm and usual care arm respectively. Twenty-one and 26 patients were in the primary and secondary prevention arm respectively. There were 28 non-Indigenous patients and 19 Indigenous patients. Participant characteristics are included in an online supplementary table.

4) It is hard to see how some of the quotes support the overarching themes identified, and the free access to meds seems to artificially lower the costs (indigenous patient 13, IHS). This is likely a reflection that the patients were enrolled in the clinical trial.

Response: This is a pragmatic trial and as such the costs of medications were to mimic real life situations. A new nationwide policy initiative was introduced during the course of the study which offered free access of medications to Indigenous patients in both arms of the study. Thus, for this group cost was unlikely to subsequently figure as a potential advantage of the polypill.

This section has now been amended to explain this more clearly in page R13, lines 256-260:

For Indigenous participants who were eligible for complete medication subsidisation through a government scheme newly introduced during the PRCT, there was no cost advantage of the polypill since treatment in both arms was subsequently free. Thus, depending on individual circumstance, the savings varied for the patients.

5) In fact, is there any concern that those in the clinical trial might be different than patients not in such a trial?

Response: Although the trial was designed to be pragmatic to reflect ‘real life’ conditions under which individuals would undergo treatment, we were aware that involvement in such a study may have affected behaviour and that a limitation of our study would be that it does not capture perspectives of patients who did not want to be in the trial. As such there were questions to providers to explore the impact of the trial on patient adherence and reasons why patients may have refused to be on the trial.
6) Many important concepts (e.g. extrinsic factors associated with adherence) are not supported by the represented quotes.

Response: An additional table with quotes to highlight the main themes have been added as an online data supplement, and more relevant quotes included in the text. Please see response to reviewer 1, comment 10. (Please see page R15, lines 327-310.)
References


SUPPLEMENTAL MATERIAL

Supplementary methods

The Kanyini GAP Study- health professionals interview guide (GP’s)

<table>
<thead>
<tr>
<th>Initial Broad Descriptive Questions</th>
<th>Probing Questions (These are a guide only. It is not expected that you ask all these questions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OVERALL VIEWS ON POLYPILL IN CVD MANAGEMENT</strong></td>
<td>To establish pre and post trial views of a general polypill strategy for CVD, as well as the specific KGAP polypill</td>
</tr>
</tbody>
</table>
| **What is your overall view of a polypill strategy in CVD management?** | - Why did you become involved in this study? i.e. motivation for taking part  
  - Experience in general being involved with the Kanyini GAP Polypill strategy/study?  
  - What experience have you had with prescribing other fixed-dose combination or multidrug component medications in cardiovascular disease? What about other therapeutic areas?  
  - Could you describe what you think are the negative/positive aspects of using a polypill strategy to manage CVD?  
    - How does this compare to other therapeutic areas?  
    - Have your views about prescribing a polypill changed since being involved in this study? Can you please describe? What did you think of the components that were in this polypill (Aspirin, BP lowering, statin)?  
  - What would be your ideal combination pill? |

**OVERALL VIEWS ON PATIENT ADHERENCE TO CARDIOVASCULAR MEDICATIONS**

- To understand conceptualisation and significance of medication adherence from prescriber perspective and what role they, other health care providers, the health system and policies play
<table>
<thead>
<tr>
<th>What are your views on patient adherence with cardiovascular disease medications?</th>
</tr>
</thead>
</table>
| - How important do you think adherence to medications is with respect to cardiovascular disease outcomes?  
  o How does this compare to other therapeutic areas?  
- Thinking in terms of a few patients who you know best who are concomitantly prescribed anti-platelets, BP lowering and lipid lowering medications, either as fixed combination pills or not, how do you think these patients perceive the function of their cardiovascular medications?  
- Do you know if your patients take their medications?  
- In your experience, what do you think are the barriers/facilitators to patients adhering with cardiovascular medications? (e.g. medicine-, patient- health system/policy-, disease-related, cultural)  
  o What role does a patient’s cultural background have?  
  o What role does current policy have?  
- What role do you think GP’s play in supporting patients to take their medications?  
  o Is the polypill helpful in doing this?  
  o Does it help you be more effective in managing CV risk?  
  o What about other staff? |

**PROVIDER SATISFACTION/ PROBLEMS WITH THE POLYPILL STRATEGY USED IN KANYINI GAP**

- To illustrate the experience with prescribing the polypill, and to compare and contrast this with experience with other cardiovascular medications. **Note:** There is a particular interest in whether there is a difference in practice for polypill group at drug initiation.  
- To understand if there was any difference in usual care management throughout the trial
| Could you describe what it has been like to look after your patients in the polypill group? | – What were the major advantages of prescribing the polypill used in Kanyini Gap?  
– What were the major disadvantages of prescribing the polypill used in Kanyini Gap?  
– What was your experience with commencing participants on the polypill?  
  o Did you change/alter treatment prior to commencing on trial?  
– Did you change or alter treatment prior to commencing patients on trial?  
  o How did this compare with your previous experience with starting cardiovascular medications?  
– How did you find tailoring your patients’ medicines when they were on the polypill?  
– How do you decide if the ingredients in the polypill are or are not enough for your patients?  
– How do you know what needs to be increased, e.g. through targets, etc.?  
– Were there any times when you were not happy with the polypill and had to change to other medicines? If so, please describe.  
– Were there any problems prescribing additional treatments?  
– How did you find assessing response to treatment for patients on the polypill?  
– Were there any terminations of patients due to unawareness of trial or new treatment, etc.?  
– In your opinion, do you think being on the trial has influenced the behaviour of patients? (i.e. re RCTs – people may be more compliant, tend to follow protocols, etc.) |
| --- | --- |
| Could you describe what it has been like to look after your patients in the usual care group? | – What was your experience in providing usual care to the participants not taking the polypill throughout the trial?  
– Did you feel that you changed your management in any way for this group during the course of the study? If so, how? |

**PATIENT SATISFACTION/ PROBLEMS WITH THE POLYPILL STRATEGY**

*To illustrate feedback given to the prescribers from patients about the polypill*

*To understand if the usual care patients reported any difference in management throughout the trial*
| What have been your patients’ impressions/thoughts about being in the polypill group? | – Did you receive any feedback from your patients about their experience in the trial? If so, please describe.  
– Do you feel that your patients were satisfied with the care they received whilst in the polypill group?  
– What were the major advantages of taking the polypill from the patient perspective?  
– What were the major disadvantages of taking the polypill from the patient perspective?  
– How well tolerated was the polypill in general?  
  o Did any of your patients experience any side-effect issues with the polypill? If so how did you manage these issues?  
– Did your patients report any problems accessing the medicines?  
  o Any problems with filling the script from the pharmacy (cost, confusion etc)?  
  o Any problems with the packaging or instructions?  
– Did your patients report any barriers to actually taking the medicines? If so, please describe  
– Is there anything else which could be done to make the treatment/polypill more effective? |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>– What have been your patients’ impressions/thoughts about being in the usual care group?</td>
<td>– Do you feel that your patients were satisfied with the care they received whilst in the usual care group?</td>
</tr>
</tbody>
</table>

**GENERAL IMPRESSIONS OF THE STUDY**

*To understand how the trial integrated into everyday practice*
<table>
<thead>
<tr>
<th>What has it been like for you to be involved in the GAP study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>‒ What was the impact on you and your health service in choosing to be a part of this trial?</td>
</tr>
<tr>
<td>‚ Did you experience any problems with the general administration of this trial? If so please explain.</td>
</tr>
<tr>
<td>‚ Were there any benefits to you or your practice as a result of participating in this trial? If so please explain.</td>
</tr>
<tr>
<td>‒ Would you be interested in participating in future clinical trials as a result of your experience with this study? If no, why not?</td>
</tr>
</tbody>
</table>

**SUITABILITY OF THE TRIAL DESIGN**

*To understand if other trial related variables may have impacted on outcomes*

<table>
<thead>
<tr>
<th>What are your thoughts about the design of the GAP polypill study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>‒ What was your experience with the screening process?</td>
</tr>
<tr>
<td>‚ Were you satisfied with the process of gathering baseline information about study participants?</td>
</tr>
<tr>
<td>‚ Were the eligibility criteria satisfactory?</td>
</tr>
<tr>
<td>‚ What did you think of using absolute risk based entry criteria?</td>
</tr>
<tr>
<td>‒ Were there any difficulties experienced in communicating study information to participants?</td>
</tr>
<tr>
<td>‒ How did you find the randomisation visit?</td>
</tr>
<tr>
<td>‒ How did you find the follow-up and monitoring of your patients?</td>
</tr>
<tr>
<td>‒ Did you experience any problems sharing/ coordinating care with providers who were not involved in the study?</td>
</tr>
</tbody>
</table>

**TRANSLATION INTO CLINICAL PRACTICE AND POLICY**

*To understand how the trial results may or may not translate into practice.*

<table>
<thead>
<tr>
<th>If found to be beneficial, what would you see as the role of the polypill in everyday practice?</th>
</tr>
</thead>
<tbody>
<tr>
<td>‒ What are your views on the use of the polypill in the study setting compared to in everyday practice?</td>
</tr>
<tr>
<td>‒ How do you think a cardiovascular polypill will impact on your day-today professional practice?</td>
</tr>
<tr>
<td>‒ If the polypill is found to be beneficial, what would be your advice to government on implementing its use in the general population?</td>
</tr>
</tbody>
</table>

**CONCLUDING QUESTIONS**
We will also be conducting some interviews with patients involved in the trial to understand their experiences. In your opinion, what areas to you think we should explore?

- Are there any aspects about medication adherence that you would specifically like explored?

- Is there anything else you would like to say that we have not talked about in this interview? i.e. about the polypill or the study?

---

### The Kanyini GAP Study- health professionals interview guide (pharmacist)

<table>
<thead>
<tr>
<th>Initial Broad Descriptive Questions</th>
<th>Probing Questions (These are a guide only. It is not expected that you ask all these questions)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Purpose of process evaluation is to establish overall views on a polypill based approach to CV risk management.</td>
</tr>
</tbody>
</table>

### OVERALL VIEWS ON POLYPILL IN CVD MANAGEMENT

To establish pre and post trial views of a general polypill strategy for CVD, as well as the specific KGAP polypill

**What is your overall view of a polypill strategy in CVD management?**

- Could you describe what you think are the negative/positive aspects of using a polypill strategy to manage CVD?
  - How does this compare to other therapeutic areas?
  - Have your views about prescribing a polypill changed since being involved in this study? Can you please describe? What did you think of the components that were in this polypill (Aspirin, BP lowering, statin)?
- What would be your ideal combination pill?

### OVERALL VIEWS ON PATIENT ADHERENCE TO CARDIOVASCULAR MEDICATIONS

To understand conceptualisation and significance of medication adherence from providers perspective and what role they, other health care providers, the health system and policies play
<table>
<thead>
<tr>
<th>What are your views on patient adherence with cardiovascular disease medications?</th>
</tr>
</thead>
</table>
| – How important do you think adherence to medications is with respect to cardiovascular disease outcomes?  
  o How does this compare to other therapeutic areas?  
| – Thinking in terms of a few patients who you know best who are prescribed anti-platelets, BP lowering and lipid lowering medications in combination, how do you think these patients perceive the function of their cardiovascular medications?  
| – In your experience, what do you think are the barriers/facilitators to patients adhering with cardiovascular medications? (eg medicine-, patient- health system/policy-, disease-related)  
| – What role do you think you play in supporting patients to take their medications?  
<p>| – How do you think the polypill strategy compares to other patient adherence aids, i.e. Webster pack? |</p>
<table>
<thead>
<tr>
<th>PROVIDER SATISFACTION/ PROBLEMS WITH THE POLYPILL STRATEGY USED IN KANYINI GAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>– To illustrate the experience with supplying the polypill, and to compare and contrast this with experience with other cardiovascular medications. Note: There is a particular interest in whether there is a difference in practice for polypill group at drug initiation.</td>
</tr>
<tr>
<td>– To understand if there was any difference in usual care management throughout the trial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Could you describe what it has been like to look after your patients in the polypill group? (drawing on your experiences)</th>
</tr>
</thead>
<tbody>
<tr>
<td>– What were the major advantages of supplying the polypill used in Kanyini Gap?</td>
</tr>
<tr>
<td>– What were the major disadvantages of supplying the polypill used in Kanyini Gap?</td>
</tr>
<tr>
<td>– What was your experience with participants commencing on the polypill?</td>
</tr>
<tr>
<td>o Do you have any examples?</td>
</tr>
<tr>
<td>o How did this compare with your previous experience with starting cardiovascular medications?</td>
</tr>
<tr>
<td>o Where there any concerns by patients in starting the polypill, i.e. concern about efficacy, change of routine, etc?</td>
</tr>
<tr>
<td>– How did you find counselling your patients about the polypill?</td>
</tr>
<tr>
<td>– Did you think that you changed your management in any way for the participants who were taking the polypill? If so, how?</td>
</tr>
<tr>
<td>– Were there any problems when additional treatments for cardiovascular disease were prescribed? i.e. need to tailor medications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENT SATISFACTION/ PROBLEMS WITH THE POLYPILL STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>To illustrate feedback given to the providers from patients about the polypill</td>
</tr>
<tr>
<td>To understand if the usual care patients reported any difference in management throughout the trial</td>
</tr>
</tbody>
</table>
| What have been your patients’ impressions/thoughts about being in the polypill group? | - Did you receive any feedback from your patients about their experience in the trial? If so, please describe.  
- Do you feel that your patients were satisfied with the care they received whilst in the polypill group?  
- What were the major advantages of taking the polypill from the patient perspective?  
- What were the major disadvantages of taking the polypill from the patient perspective?  
- How well tolerated was the polypill in general?  
  - Did any of your patients experience any side-effect issues with the polypill? If so how did you manage these issues?  
- Did your patients report any problems accessing the medicines?  
  - Any problems with filling the script from the pharmacy (cost, PBS safety net, confusion etc)?  
  - Any problems with the packaging or instructions?  
- Did your patients report any barriers to actually taking the medicines? If so, please describe |
<table>
<thead>
<tr>
<th><strong>GENERAL IMPRESSIONS OF THE STUDY</strong></th>
<th><strong>To understand how the trial integrated into everyday practice</strong></th>
</tr>
</thead>
</table>
| **What has it been like for you to be involved in the GAP study?** | What was the impact on you and your health service in choosing to be a part of this trial?  
  ○ Did you experience any problems with the general administration of this trial? If so please explain.  
  ○ Were there any benefits to you or your pharmacy as a result of participating in this trial? If so please explain.  
  – Would you be interested in participating in future clinical trials as a result of your experience with this study? |

<table>
<thead>
<tr>
<th><strong>SUITABILITY OF THE TRIAL DESIGN</strong></th>
<th><strong>To understand if other trial related variables may have impacted on outcomes</strong></th>
</tr>
</thead>
</table>
| **What are your thoughts about the design of the GAP polypill study?** | Were there any difficulties experienced in communicating study information to participants?  
  - Did you encounter any difficulties when the polypill patients were new to your pharmacy?  
  - Did you experience any problems sharing/coordinating care with providers who were not involved in the study? |

| **TRANSLATION INTO CLINICAL PRACTICE AND POLICY** | **To understand how the trial results may or may not translate into practice.** |
If found to be beneficial, do you think the polypill could be used in everyday practice?

(Last is the magic wand Q...)

- What are your views on the use of the polypill in the study setting compared to in everyday practice?
- How do you think a cardiovascular polypill will impact on your day-to-day professional practice?
- If the polypill is found to be beneficial, what would be your advice to government on implementing its use in the general population?

**CONCLUDING QUESTIONS**

- We will also be conducting some interviews with patients involved in the trial to understand their experiences. In your opinion, what areas do you think we should explore?
- Are there any aspects about medication adherence that you would specifically like explored?
- Is there anything else you would like to say that we have not talked about in this interview?
The Kanyini GAP Study- Patient interview guide

Purpose of the interview: *Capture what it is like for people to manage CVD and how to manage their tablets, and how the burden of taking tablets in daily life could be made easier/better/worse. How a polypill might influence this (or not); or how the trial might influence this (or not).*

| Area of Interest | Initial Broad Descriptive Questions | Possible Probing Questions  
(These are a guide only. Depending on what the patient tells you, you do not have to ask all these questions or use the words exactly as written.) |
|------------------|-------------------------------------|-------------------------------------------------------------------|
| Health care experience | Can you tell me about your health care since you've been on the trial? | o How is your health in general?  
o What are some of the good/bad things about your health care?  
o Are there differences or similarities with your health care since you've been part of this study compared to usual care?  
  o And compared to other illnesses?  
o What type of support do you get from family, community or social groups with looking after your health?  
  o What kind of roles/responsibilities do you have in your family? |
<table>
<thead>
<tr>
<th>Satisfaction/ problems with the polypill strategy</th>
<th>What are your thoughts about your current treatment for your heart?</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Do you know the 4 medications in the polypill and what they’re for? (Aspirin, BP lowering x2, statin (lipid lowering/cholesterol, etc.)</td>
<td></td>
</tr>
<tr>
<td>o How do you find the tablets you are taking?</td>
<td></td>
</tr>
<tr>
<td>o What do you think are the major advantages of your current treatment (polypill or usual medications)?</td>
<td></td>
</tr>
<tr>
<td>o What do you think are the major disadvantages of your current treatment (polypill or usual medications)?</td>
<td></td>
</tr>
<tr>
<td>▪ What things would worry you about changing your usual medications?</td>
<td></td>
</tr>
<tr>
<td>o Would you be happy to continue taking your current treatment (polypill or usual medications)?</td>
<td></td>
</tr>
<tr>
<td>o What might happen that would make you change from taking the polypill or your usual meds?</td>
<td></td>
</tr>
<tr>
<td>o What problems have you experienced with your current treatment (polypill or usual medications)? (i.e. side effects, cost issues)</td>
<td></td>
</tr>
<tr>
<td>o How can your doctor improve your current treatment?</td>
<td></td>
</tr>
<tr>
<td>o What sort of support do you get in managing your blood pressure, cholesterol, etc?</td>
<td></td>
</tr>
<tr>
<td>Medication taking behaviour</td>
<td>Many people find it difficult to take their medications everyday. Has there been a time when you haven’t been able to take your medications every day? OR What suggestions would you give to people, who do struggle with taking medications, i.e. what has worked for you?</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>- How many pills do you take a day?</td>
</tr>
<tr>
<td></td>
<td>- How easy do you find taking your medications?</td>
</tr>
<tr>
<td></td>
<td>o What are the things that help you to take your medications? (i.e. family, Webster pack, other memory aids, time of day, etc.)</td>
</tr>
<tr>
<td></td>
<td>o How would you know if you’ve not taken your medication?</td>
</tr>
<tr>
<td></td>
<td>- When do you find it more difficult to take medications?</td>
</tr>
<tr>
<td></td>
<td>o What are the things that might make you stop taking a medication?</td>
</tr>
<tr>
<td></td>
<td>- What other things might change the way you take your medications?</td>
</tr>
<tr>
<td></td>
<td>- Can you describe any time or situation when you didn’t want to take your medications?</td>
</tr>
<tr>
<td></td>
<td>o What things were influencing your decision?</td>
</tr>
<tr>
<td></td>
<td>- Who would you speak to if you were having trouble with your medications?</td>
</tr>
<tr>
<td></td>
<td>o When have you had to do this?</td>
</tr>
<tr>
<td></td>
<td>- Which of your medications do you think are the most important to you and why?</td>
</tr>
<tr>
<td></td>
<td>- How do you usually get your supply of medications?</td>
</tr>
<tr>
<td></td>
<td>- Have there been times when you share medications with family members?</td>
</tr>
<tr>
<td></td>
<td>- Have there been times when you halve tablets, or just take them on alternate days for example?</td>
</tr>
<tr>
<td></td>
<td>o What has been the main reason/s for this?</td>
</tr>
<tr>
<td>What has your experience been with taking medications throughout this study?</td>
<td>o How has your experience with taking your medication/s in this study been different / similar to the way you would usually take medications?</td>
</tr>
<tr>
<td></td>
<td>o In what ways has this study changed the way you take your medications?</td>
</tr>
<tr>
<td></td>
<td>o What things have made it easier or harder for you to take your medications while being involved in this study?</td>
</tr>
<tr>
<td></td>
<td>o Has the cost of medications been an issue for you?</td>
</tr>
<tr>
<td></td>
<td>o Have other costs, e.g. cost of attending GP, travel to the health service, other specialist services, etc. been an issue?</td>
</tr>
<tr>
<td>Translation to current practice</td>
<td>What has helped/prevented you from taking your medications throughout this study that might be different to everyday life? <em>(e.g. without being monitored as much as during the trial)</em></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• Now that the study is over, what things might change the way you take your medications (polypill or usual medications)?</td>
</tr>
<tr>
<td></td>
<td>○ Do you think you would be able to take your current treatment in the same way that you have throughout the study?</td>
</tr>
<tr>
<td></td>
<td>• What other things would help you take your medications?</td>
</tr>
<tr>
<td></td>
<td>○ What type of support from nurses/health workers/AMS might assist you in taking your medications?</td>
</tr>
<tr>
<td></td>
<td>○ What can the government/doctors/pharmacists do to help?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General views about the trial</th>
<th>What are your thoughts about the Kanyini Gap study in general?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• How have you found being involved in the study?</td>
</tr>
<tr>
<td></td>
<td>○ What things did/didn’t you like about being involved?</td>
</tr>
<tr>
<td></td>
<td>• Tell me how you think the study worked, and what it was hoping to achieve?</td>
</tr>
<tr>
<td></td>
<td>• What were the things that made you want to participate in the study initially?</td>
</tr>
<tr>
<td></td>
<td>○ What were the benefits to you of participating?</td>
</tr>
<tr>
<td></td>
<td>• What concerns did you have about participating in this study?</td>
</tr>
<tr>
<td></td>
<td>○ Were there any things that may have stopped you from participating initially?</td>
</tr>
<tr>
<td></td>
<td>○ What were the risks of participating in the study?</td>
</tr>
<tr>
<td></td>
<td>• Once you were enrolled, what would have changed your mind about being in the study?</td>
</tr>
<tr>
<td></td>
<td>○ Did you feel that you could withdraw at any time?</td>
</tr>
<tr>
<td></td>
<td>• Did you know who to contact if you had any concerns about the trial?</td>
</tr>
<tr>
<td></td>
<td>• What were your thoughts about your privacy throughout this study?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concluding questions</th>
<th>Are there things which we can do better to improve the study or the running of the trial?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Is there something else that you would like to say, that we have not talked about in this interview?</td>
</tr>
</tbody>
</table>
## Supplementary Tables

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>POLYPILL</th>
<th>USUAL CARE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>22</td>
<td>25</td>
<td>47</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>67.1 (8.4)</td>
<td>63.9 (10.3)</td>
<td>65.4 (9.5)</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>10 (46%)</td>
<td>12 (48%)</td>
<td>22 (47%)</td>
</tr>
<tr>
<td>Aboriginal/ Torres Strait Islander</td>
<td>6 (27%)</td>
<td>13 (52%)</td>
<td>19 (40%)</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>12 (55%)</td>
<td>9 (36%)</td>
<td>21 (45%)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>10 (46%)</td>
<td>16 (64%)</td>
<td>26 (55%)</td>
</tr>
<tr>
<td>Drug treatment (at baseline)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Category</td>
<td>ARIA 1</td>
<td>ARIA 2</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td><strong>High-risk primary prevention</strong></td>
<td>Yes to all 3 (BP lowering, aspirin and statin)</td>
<td>7 (18%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td></td>
<td>No to all 3</td>
<td>5 (23%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td>Yes to all 3 (BP lowering, aspirin and statin)</td>
<td>7 (18%)</td>
<td>15 (60%)</td>
</tr>
<tr>
<td></td>
<td>No to all 3</td>
<td>3 (14%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td><strong>Health service</strong></td>
<td>Indigenous health services (Aboriginal community controlled and government-run)</td>
<td>8 (36%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td></td>
<td>General Practice</td>
<td>14 (64%)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td><strong>Accessibility/Remoteness Index of Australia (ARIA)</strong></td>
<td>ARIA 1</td>
<td>15 (68%)</td>
<td>15 (68%)</td>
</tr>
<tr>
<td>ARIA 2-3</td>
<td>7 (32%)</td>
<td>10 (45%)</td>
<td>17 (36%)</td>
</tr>
</tbody>
</table>

* SD Standards deviation BP Blood pressure † ARIA 1: metropolitan and inner regional  ARIA 2-3: outer regional and remote
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GP*</th>
<th>Pharmacist</th>
<th>AHW/Nurse*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>25</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Age groups †2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-39 (%providers)</td>
<td>5 (11%)</td>
<td>5 (11%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>40-69</td>
<td>18 (38%)</td>
<td>7 (15%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Male Gender (%providers)</td>
<td>15 (32%)</td>
<td>10 (21%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Years practicing (median, range)</td>
<td>25 (2 to 35)</td>
<td>13 (2.5 to 32)</td>
<td>3 (0.5 to 17)</td>
</tr>
<tr>
<td>Years at site (median, range)</td>
<td>11.5 (0 to 30)</td>
<td>6 (0 to 12)</td>
<td>1 (1.2 to 17)</td>
</tr>
<tr>
<td>Formal cross-cultural training (%providers)</td>
<td>18 (38%)</td>
<td>3 (6%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Adherence support services offered</td>
<td>n/a</td>
<td>10</td>
<td>n/a</td>
</tr>
<tr>
<td>Health Service</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indigenous Health Service (%providers)</td>
<td>16 (34%)</td>
<td>n/a</td>
<td>9 (19%)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------</td>
<td>-----</td>
<td>---------</td>
</tr>
<tr>
<td>General Practice (%providers)</td>
<td>10 (21%)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Accessibility/Remoteness Index of Australia (ARIA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIA 1 (%providers)</td>
<td>16 (34%)</td>
<td>9 (19%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>ARIA 2-3 (%providers)</td>
<td>10 (21%)</td>
<td>4 (9%)</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

* GP General Practitioner AHW Aboriginal health Worker SD standard deviation † Missing data n=3

Table 3

**Major Codes and their descriptions**

**Adherence**
This includes references to, comments from providers and patients on all aspects of patient adherence to medications such as strategies of using a routine, having the medications in a dose administration pack. This also includes observation of risks of non-adherence, (i.e. death, effects on family/community.) The burden of the number of medications and the complexity of medication regimes contributed to intentional non-adherence at times.

**Being well**
‘Being well’ is described through comments, attitudes, perceptions of patients' own general health, i.e. physical and emotional well-being, self-care and lifestyle risk factors, other health issues, and protective/ supportive mechanisms in place such as family and community support.

**Good care**
This covers patient satisfaction with health care provision, such as accessibility to health care and other support services, and the provider-patient relationship. It also includes the collaboration between providers, pharmacists and IHSs.

**Health literacy**
Health literacy includes patients’ knowledge of the importance of adherence to medications, including how, when, why to take medications and their efficacy, etc. It also includes analysis of data around health seeking behaviour, i.e. patients’ motivation to find out about their condition and to seek treatment, and also the ‘missed dose effect’.

**Acceptability of the Polypill**

This code included descriptions of what were the advantages and disadvantages of the polypill strategy. Many of the patients liked the advantages of the ease and convenience because of the reduced number of tablets, single dosing, and cost savings was also listed as positive. Other advantages from the providers’ point of view included being more aware of the participants’ absolute risk and starting the patients on the three types of medications instead of taking the time to titrate to all medications. However, being unable to titrate and tailor the medications was listed as disadvantages. Most of the providers suggested having other possible polypill combinations.

**‘Real World’**

This code contained views from both patients and providers in regards to what they hoped to see after the trial. The responses varied from the polypill being just another ‘combination’ medication out there, to potentially being disappointed if it was not on the shelf, and that the polypill would be ideal only in certain circumstances, e.g. for primary prevention. Many of the providers and patients from the IHSs expressed the understanding and support for the polypill for the Aboriginal population given the higher incidence, possible limited literacy and difficulty in taking many medications.

**Financial Considerations**

The majority of patients reported knowing they have to spend the money on medications and health care, and would do so to improve their health. A number of policies are in place to reduce the cost of medications and health care for all Australians and these were mentioned often by the patients and pharmacists.

**Aboriginal Health Considerations**

This code contained views from patients and providers which specifically mentioned factors and issues concerning Aboriginal health such as burden of disease, access to culturally safe health services, role of the community and family in maintaining adherence.

Table 4: Further examples of quotes illustrating the results

**Themes/ subthemes and further examples of the quotes**
Acceptability of the polypill in improving adherence

Ease and convenience

(My daughter) is very happy for me because I’ve never been used to taking tablets and I always find them a bit difficult to take. Because it’s a capsule and because it’s only one, she said “I’m very happy for you mum because it will be so much easier”. (Patient 17, urban GP clinic)

Cost savings

I think (the trial) was trying to achieve (for) people possibly forgetting medication and it’s all in the one pill so therefore they don’t have to think I’ve got five pills to take, six pills to take, it’s all going to be one. I thought that was the main thing and another thing was cost to people that, like myself that are aged pensioners, most people are struggling to live, we’re not you know, because we own the house and things, we own everything, but I mean things could change. But I thought those were the two important things. (Patient 41, urban GP clinic)

Adherence depends on other factors

Wanting to be well

As I said I just used to take my tablets all the time and it was just a routine. If you want better health you’ve got to take your medication and things like that. (Patient 23, regional GP clinic)

Importance of family

(My grandson) comes and reminds me, he says “Nan, have you had your needle yet?” and that’s good for me too because sometimes I don’t remember, and my partner will say “have you taken your tablets today? (Patient 1, urban IHS)

Good Care

I’d like to see in rural and remote areas more indigenous specific mental health issues and programs and that. More around narrative therapy than cognitive therapy. Because cognitive therapy don’t work for our mob. Because we’re story tellers. So we’d rather sit down and talk and tell our stories and get to the basis of the issues. Rather than say okay, you get depressed when this happens, let’s teach you how to handle it. To me that’s a bandaid treatment. So because I know with, with the studies that I’ve done, mental health could also play a lot on the heart issues. And cholesterol and all that other type of stuff too.... A holistic approach to health. Not just saying okay, we’ve got mental health over here and general health over here. Get the two of them somehow working together (Patient 30, remote IHS)

You will know that I can guarantee that the majority of our people if we’re getting signs of heart attack, shortness of breath, we’ll ring GP, we’ll ring an Aboriginal medical centre before we actually go, even call, think about even calling an ambulance because of the fact that how we’re
going to be treated, how we're going to be spoken to over the phone. (AHW 26, urban IHS)

[I talk to my doctor about my medications because] I suppose I have certain ways of doing things. If I have a problem I like to be systematic and analyse why it went wrong and if I fix it, will it go wrong again. (Patient 16, urban GP clinic)

Importance of health literacy

When I question them and quiz them and say you know “how’s your cholesterol going, is everything okay?” they just don’t know. So at the end of the day again there’s a lack of communication occurring somewhere along the line, so if they knew that they were taking a Polypill that was going to keep their blood pressure, cholesterol, thin their blood, do all that sort of stuff, then potentially they’d be more inquisitive to make sure that it was doing what it was supposed to be doing. (Pharmacist 13, pharmacy related to urban GP clinic)

Policies impacting healthcare costs

Reduce the cost of them. Especially when you’re on a lot like I am… a lot of people you know, pensioners are saying, it’s just terrible that they do go without (their medications) sometimes because they just can’t afford it. (Patient 27, urban GP clinic)

Polypill in patient management

Limitations of a fixed dose combination

I think patients would need to be advised, or doctors would need to be advised to start the individual components of the polypill individually to start with to make sure there’s not side effects, and then start the patient on it in the future because then you can be certain that there’s no individual side effects to the different components. (GP 43, remote IHS)

Adequacy of the Polypill Components

The fixed dose combination was fine, but then you’re adding on extra medications as well, so, to get someone up to 80 of Simvastatin and so that sort of minimises some of the benefits of actually being on polypill because you’re adding in extra medications anyway...There were often, the decisions around polypill were actually harder than I was expecting rather than just a great concept and you put them on polypill, there was often quite a lot of thought about how you’re switching statins. I think one guy we even had strangely on a mixture of two statins because of what he was on before and what was in the polypill. (GP 8, urban IHS)
Other combinations in the future

I think having a wider range of dosages. The concept’s brilliant and the patients actually really enjoyed being on it. They really like having just one tablet. The feedback was consistently good from the patients, that they liked the concept of everything rolled into one. So having flexible dosages, a wider range of different choices would be a way round that. (GP 37, regional GP clinic)

Who could it be suitable for?

High-risk primary prevention patients

I think the one difficulty when faced with a patient who really doesn’t have much health literacy and much knowledge about their own cardiovascular risk one of the difficulties is convincing them that they need to be – will end up needing to be on four or five medications when they’ve been on none and I think a polypill is generally a very useful tool for doing that. (GP 27, IHS)

A strategy to address CVD burden of disease in Indigenous patients

I mean when you see the people that are dying around you … the same age as you and even younger, it’s all to do with health that they died not taking medication. Maybe if they were given the one pill instead of taking half a dozen they might be still here today. (Patient 4, urban IHS)

Well I think it could have significant impacts on Aboriginal health if it were to be introduced as a generally available medication. And I think we can’t underestimate how much it may make some change because we do know that cardiac disease is the major cause of Aboriginal mortality. And I think if it’s made easier to manage then you know, the impacts could be significant so and I think generally for the general population as well. But I think if there were a public policy imperative as to try to positively affect Aboriginal mortality then this is one approach that will aid that. (GP 23, urban IHS)

I still think it’s not going to benefit the people that probably need the most benefit. So I think in some ways it’s not necessarily addressing the equity gap because those that are most disadvantaged and most at risk are not going to be the ones that would benefit from this treatment, from this particular polypill. But from other polypills I don’t know, maybe they would. (GP 40, remote IHS)
Supplementary Figure

**PEAK Coding Framework**

**BEING WELL**
- self care
- general health
- family and community support
- stress

**GOOD CARE**
- provider-patient relationship
- access to health services
- other support services

**HEALTH LITERACY**
- health-seeking behavior
- missed dose effect

**TRIAL IMPACT**
- current treatment
- patient management
- effects on services, (e.g. bottom line, time)
- effects on patient, (e.g. changes in med-taking behavior, increased health awareness)
- tailoring of meds

**RESEARCH MOTIVATION**
- greater good
- personal good

**ADHERENCE**
- strategies for adherence
  - complexity
  - burden of pills
  - drug holiday

**ACCEPTABILITY OF PP**
- advantages: less tabs, ease, convenience, cost
- disadvantages: fixed combination, side effects, tailoring of meds

**ABORIGINAL HEALTH CONSIDERATIONS**
- social justice
- determination
- cultural safety

**REAL WORLD**
- Population Health Approach
  - use of absolute risk
  - primary prevention
  - ‘ideal patient’
- ‘On the shelf’
  - policy implications
  - future PP combinations

**FINANCIAL CONSIDERATIONS**
- CTG, policy, PBS, Safety Net
- cost of meds & health care